Pupil size in diabetes

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Abstract
Sympathetic function was studied in 101 diabetic children and 102 age and sex matched control children, as part of a longitudinal study of the evolution of microvascular disease in the population of diabetic children and adolescents in Avon County. The median (range) age of the diabetic population was 13·5 (6·0–17·2) years, the duration of diabetes was 4·0 (0·4–13·9) years, and glycated haemoglobin (HbA1) was 10·9 (7·0–18·1)%.

Pupillary adaptation in darkness, as an index of sympathetic neuropathy, was measured using a Polaroid portable pupillometer. Diabetic children had a significantly smaller median pupillary diameter, measured as the pupil/iris ratio and expressed as a percentage, than control children (median (range) 62·9 (50·3–72·1) v 65·9 (52·2–73·8)). Pupillary diameter was significantly related to diabetes duration ($r=-0·22$), HbA1 ($r=-0·34$), systolic blood pressure ($r=-0·25$), diastolic blood pressure ($r=-0·49$), and mean albumin/creatinine ratio on random urine samples ($r=-0·26$). Pupillary diameter was not related to age ($r=-0·1$). Eight (7·9%) diabetic and four (3·9%) control children were identified as having abnormal pupillary dilation in darkness. In comparison with the rest of the diabetic population, these diabetic children had longer diabetes duration and poorer glycaemic control.

Polaroid pupillometry has demonstrated subclinical autonomic neuropathy in a population of diabetic children and adolescents. These abnormalities were related to poor metabolic control, long diabetes duration, and also to other indices of microvascular disease.

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The Avon childhood diabetes study is a prospective study of a geographically defined population of diabetic children, designed to describe the evolution of microvascular and neurological abnormalities.

Autonomic nervous dysfunction in adults with diabetes has been defined by small pupil size[1] and impaired pupillary response to darkness[2] or light.[3] There are two previous studies on pupillometry in children[4] and adolescents,[5] reporting reduced pupillary adaptation in darkness, early in childhood diabetes. Pupillary measurements have also been used in conjunction with cardiovascular tests,[6 7] as indices of autonomic neuropathy.

There are conflicting reports among adults with diabetes on the correlations between pupillary diameter in darkness and duration of diabetes or metabolic control: some investigators report negative correlation[5 8 9] of pupil size with these variables, whereas others show no correlation.[4 10] Pupil size in darkness has been shown in adults to be negatively related to vibratory sensation threshold,[11] while patients with frank diabetic retinopathy or nephropathy are reported to have smaller pupillary diameter than patients without these complications.[9]

The present study describes the prevalence of sympathetic dysfunction in a geographically defined population of diabetic children and adolescents and the influence of such factors as diabetes duration and glycaemic control.

Subjects and methods
SUBJECTS
At the time of initiating this study (June 1986) 196 children with insulin dependent diabetes mellitus (IDDM) were identified as living in Avon County. The following sources of population identification were used: consultant patient lists, patient lists of all 542 general practitioners in Avon County, list of diabetic children under community medical officers, computerised data on hospital admissions with the diagnosis of IDDM in hospitals of Avon County, and Bristol parents' support group.

Altogether 150 diabetic children were eligible and were asked to participate. Forty six children were ineligible because of additional illness, specific requests from the children's doctors that they should not be asked to participate, or they did not attend the consultant diabetic clinics in Bristol.

From the 150 eligible diabetic children, 129 agreed to participate in the first (D1) and 114 in the second study period (D2). One hundred and twenty nine best friend non-diabetic control children participated at D1; 15 controls declined to repeat the measurements during the second study period: consequently an additional 15 age and sex matched controls were recruited for D2. Thus a total of 144 control children participated in the two study periods.

The 46 excluded diabetic children did not differ in mean age, duration of diabetes, or glycaemic control from the participants in the Avon study. However, when comparing the 114 diabetic children who participated in both study periods with those who refused to participate in D2, the percentage of children with long diabetes duration (>5 years) or poor glycaemic control (glycated haemoglobin (HbA1) >+1 SD) was increased among the refusers.

The diabetic children were asked to identify a best friend who was of the same sex and born within the same year. The best friend was considered an appropriate control for the

following reasons: (1) the friend would be of the same age, sex, and probably of similar social class. (2) A friend is a more suitable control than a sibling (as used in many previous studies[12]); the sibling may have similar hereditary predispositions to the proband, will not be of the same age and may or may not be the same sex.

Pupillometry was performed as part of the second set of measurements only. Children below 6 years of age were not studied as they had difficulty in cooperating with the study protocol. Altogether 101 of the diabetic children and 102 of the controls provided technically acceptable (see methods section) pupillary photographs.

The median (range) age of the diabetic children was then 13·5 (6·0–17·2) years and the diabetes duration was 4·0 (0·4–13·9) years. The male to female ratio for both diabetic and control children was 0·8.

The children received no drugs apart from insulin and none had symptoms of clinical autonomic neuropathy.

METHODS

Studies on pupillometry have generally used infrared television techniques,[2 5 10] which provide direct and continuous measurement of the pupil size in complete darkness. We have used the simple Polaroid photographic technique described by Smith and Dewhirst in 1986,[13] which has been shown to correlate well with the television method.

Pupillary dilation in darkness of both diabetic and control children was estimated using a Polaroid portable pupillometer with a 75 mm lens with an incorporated electronic ring flash. The camera gave immediate colour prints. The left eye was photographed first. The right eye was photographed after an interval of 15 minutes (time for the constriction caused by the first flash to disappear[13]).

The criteria for the definition of acceptable pupillary photographs were the following: the iris should appear round, rather than oval elliptical shape, and the upper eyelid should be clear of the upper pupil margin. The pupil and iris sizes were measured in the horizontal plane on the pictures, and the pupillary diameter, measured as the pupil/iris ratio, was estimated for each eye and expressed as a percentage.[13]

The scoring of the photographs was performed 'blindly' by a single observer. No difference was observed between light (blue/grey) and dark coloured irises. For each child, the mean pupillary diameter of the left and right eye was used for analysis.

In addition, the following sets of measurements were made at both study periods:

(i) Heart rate variability, using an electrocardiograph attached to an oscilloscope and a Commodore Pet microcomputer.[14]

(ii) Vibration sensation threshold on lower limbs was estimated using a biothesiometer (Bio Medical Instrument).

(iii) Urinary albumin/creatinine ratios on aliquots from all voidings of urine over the previous 48 hours. Urinary albumin concen-

tration was estimated by an immunoturbidimetric technique using the Cobas kit.[15]

(iv) Blood pressure, using a random zero sphygmomanometer. Diastolic blood pressure was taken as Korotkoff phase IV and V.

(v) The fall of systolic blood pressure upon standing. A blood pressure fall of 30 mm Hg was defined as abnormal.[16]

Glycaemic control on the diabetic children was assessed by:

(i) HbA1 using the Coening electroendoosmosis technique.[17] The normal range for our laboratory was 5·5–7·5%. HbA1 measurements during the time of each data collection, as well as the mean HbA1 of seven three monthly measurements over a period of 18 months time, were used for analysis.

(ii) Seven point blood glucose profile on filter paper, collected on one day during the week before the day of the hospital measurement. The mean of the seven blood glucose concentrations was estimated. Capillary blood glucose concentration was estimated using the glucose oxidase technique.

The Bristol and Weston, Southmead, and Frenchay Health Authority ethical committees approved the study and participants gave written consent.

STATISTICAL ANALYSIS

The pupillary diameter, heart rate variables, and blood pressure variables were not normally distributed according to the Kolmogorov-Smyrnov test,[18] therefore non-parametric statistics were used.

The between eye coefficient of variation of pupillary diameter was estimated as follows. We estimated the pooled within individual SD:

$$SD = \sqrt{\frac{\Sigma d^2}{2n}}$$

(d=pupillary diameter difference between left and right eye; n=numbers of cases). The mean of the left and the mean of the right eye was summed and divided by two. The coefficient of variation (CV%) between individual eyes was then estimated as follows:

$$CV\% = \frac{SD}{Mean} \times 100$$

For comparisons between diabetic and control children, Mann-Whitney U test was used. For estimation of correlations, Spearman's correlations, together with partial correlation coefficients, were used.

For comparison of pupillary adaptation among groups of diabetic children with different levels of glycaemic control (good, moderate, poor) the Kruskal-Wallis one way analysis of

Table 1 Characteristics of the diabetic population

	Median (range)
Age (years)	13·5 (6·0–17·2)
Duration (years)	4·0 (0·4–13·9)
Age at diagnosis (years)	8·6 (1·4–15·5)
Dose of insulin (U/kg/day)	0·8 (0·2–1·4)
Mean HbA1 (%)	10·9 (7·0–18·1)

variance was used. The diabetic children with good control has a mean HbA1 over the 18 months of the observation period which was less than -1 SD below the mean HbA1 of the total diabetic population (that is, HbA1 $<8\cdot9\%$). Similarly the group of diabetic children with poor control had mean HbA1 $>+1$ SD (that is, HbA1 $>13\cdot3\%$). A 5% level of significance was used throughout the study.

Pupillary diameter was not age related. As pupillary diameter was not normally distributed, we used empirical centiles for the estimation of reference limits, using the SPSS-X computer package. The lowest 5% level was identified from the measurements of the control group (cut off point of normality: $56\cdot85$).

Results
A total of 101 diabetic children (88·5%) and 102 control children (89·5%) provided acceptable pupillary photographs in darkness. Their median (SD) (range) age was $13\cdot5$ $(2\cdot9)$ $(6\cdot0-17\cdot2)$ years. The demographic and glycaemic characteristics of the diabetic populations are shown in table 1.

The diabetic children, as a group, had impaired pupillary adaptation in darkness, showing significantly ($p=0\cdot0001$) smaller median pupillary diameter (median (SD): $62\cdot9$ $(4\cdot3)$, range: $50\cdot3-72\cdot1$) than the control children (median (SD): $65\cdot9$ $(4\cdot3)$, range: $52\cdot2-73\cdot8$). There was no difference in pupillary ratios between left and right eyes. All diabetic and control children had both eyes photographed in order to test the reproducibility of the method. The between eyes CV% of pupillary diameter was 2·4%.

Pupillary diameter was unrelated to age in the diabetic and control populations (table 2). In diabetic children, mean pupillary diameter was negatively related to duration of disease ($r=-0\cdot22$, $p=0\cdot025$) and to indices of glycaemic control (HbA1: $r=-0\cdot33$, $p=0\cdot001$) (fig 1). When performing the partial correlations of pupillary diameter with HbA1, controlling for diabetes duration, the strength of the correlation was reduced but still remained significant ($r=-0\cdot29$, $p=0\cdot01$).

The role of diabetes duration and glycaemic control in the development of sympathetic dysfunction were further investigated by studying the pupillary adaptation among different groups of diabetic children, using the Kruskal-Wallis one way analysis of variance.[19] When dividing the population according to HbA1 levels into groups with good, moderate, or poor control, the group with the smallest mean pupillary diameter was the one with the poorest control (HbA1 $>+1$ SD), whereas the group with the best adaptation in darkness was the one with moderate control.

Correlations were sought between pupillary diameter and other measures of microvascular disease. Pupillary diameter was negatively related to systolic blood pressure ($r=-0\cdot25$, $p=0\cdot01$) and diastolic blood pressure phase IV ($r=-0\cdot49$, $p=0\cdot001$). This correlation was unaffected, when controlling (partial correlation) for the effect of age. No such correlation

was found between pupillary diameter and blood pressure in control children.

Pupillary adaptation in diabetic children was also related to urinary albumin/creatine ratio. Thus a negative correlation was found between pupillary diameter and the mean ratio of random urine samples ($r=-0\cdot26$, $p=0\cdot008$); this was not present in the control population. When controlling (partial correlation) for HbA1 the correlation became insignificant, whereas when controlling for diabetes duration, the strength of the correlation was reduced, but still significant.

In the diabetic children the pupillary diameter correlated with blood pressure response to standing ($r=0\cdot20$, $p=0\cdot04$). Among the cardiovascular tests, it correlated only with heart rate variation while resting ($r=-0\cdot19$, $p=0\cdot049$). There were no significant correlations of pupillary diameter with other heart rate parameters or indices of autonomic and microvascular function in the control subjects.

From the measurements of pupillary diameter on control children, the 95% reference limits were estimated. Thus the diabetic and control children with a mean pupillary diameter lower than the lower reference limit were identified as having abnormal pupillary dilation in darkness (fig 2). Eight diabetic children (7·9%) and four control children (3·9%) were found to have a pupillary diameter below the reference limit. Table 3 shows the major differences between the diabetic children with an abnormal pupillary diameter and the rest of the diabetic population. These eight children were similar in age but had longer diabetes duration (median duration: 9·2 years v 3·7 years; $p=0\cdot004$) and poorer glycaemic control (median HbA1: 12·6% v 10·9%; $p=0\cdot028$), compared with the remaining diabetic population. The control children identified as having abnormal pupillary dilation were significantly older (median age: 16·1 years) than the rest of the control population.

The diabetic children with impaired pupillary adaptation to darkness also had increased diastolic blood pressure phase IV $>+2$ SD above the mean and their urinary albumin/creatine ratios were significantly raised, compared with the rest of the diabetic children (median SD scores: $+1\cdot4$ v $+0\cdot5$; $p=0\cdot002$).

One of the eight diabetic children with abnormal pupillary dilation also demonstrated abnormalities in three out of five heart rate tests during both study periods. This child was classified as having combined sympathetic and parasympathetic dysfunction.

Discussion
This study has shown that abnormalities in pupillary adaptation to darkness present early in childhood diabetes and are related to other candidate indices of early neuropathy and microangiopathy, such as reduced heart rate variability, raised blood pressure, and increased urinary albumin excretion.

Table 2   Correlation coefficients for pupillary adaptation
in darkness for diabetic and control populations
(Spearman)

	Diabetic children		Control children	
	r	p Value	r	p Value
Age	−0·09	NS	−0·02	NS
Duration	−0·22	0·025	–	–
HbA1	−0·33	0·001	–	–
Blood pressure				
Systolic	−0·25	0·010	0·11	NS
Diastolic	−0·49	0·001	0·08	NS
Albumin/creatinine ratio				
of random urine	−0·26	0·008	−0·001	NS

Previous studies on pupillometry have been performed on adult subjects and have used infrared television pupillometers. The Avon study is the first to screen for autonomic neuropathy in a geographically defined population of diabetic children and their age and sex matched controls. The population of Avon County was considered a suitable sample for longitudinal study of diabetes complications as it involves children from all social classes and from urban and rural areas. The 46 non-eligible diabetic children did not differ in mean age, diabetes duration, or glycaemic control from the participants of the Avon study; thus the prevalence of impaired indices of microvascular disease are unlikely to have been affected by their exclusion from the study.

A simple Polaroid photographic technique[13] was used for the estimation of pupillary adaptation in darkness. The method was easy to perform (except among the youngest age group (<6 years) who were unable to cooperate with the procedure), used portable equipment, and gave immediate results. The flash power was strong but tolerable: only one girl refused to repeat the picture after having experienced the brightness of the flash.

Previous studies in adults have shown that diabetic patients have smaller pupil diameters in darkness compared with controls.[2 9] There are two previous studies on pupillometry in children and adolescents with IDDM.[4 5] The first used a Polaroid pupillometer,[4] while the second used infrared computerised pupillometer.[5] In agreement with both studies, the Avon childhood diabetes study has shown that diabetic children and adolescents have reduced pupillary adaptation in darkness and that this is not a function of age.

The effect of diabetes duration on the development of autonomic abnormalities has been studied in adults, but the results are conflicting. Hreidarsson showed in diabetic subjects aged 25–43 years that pupil size
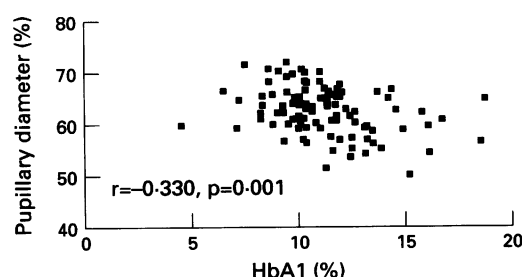

Figure 1   Scatterplot of correlation between HbA1 and pupillary diameter of the diabetic population.
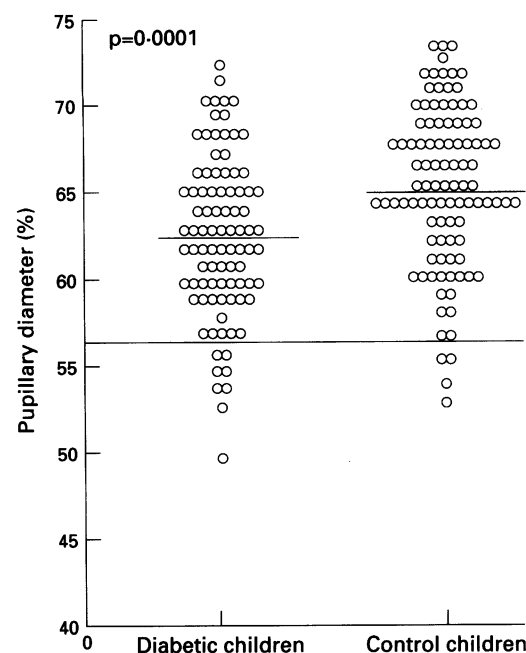

Figure 2   Pupillary diameter in darkness of the diabetic and control populations (horizontal bars=mean values).

decreased gradually with increasing duration of disease.[19] In fact they showed a rate of diminution of pupil size of about 2% per year. Conversely Smith et al showed no correlation between pupillary abnormalities and diabetes duration in a group of adult diabetic patients, aged 16–62 years.[10]

In diabetic children and adolescents, Schwingshandl et al reported a significant negative correlation between resting pupillary diameter and diabetes duration ($r=-0.29$, $p=0.0006$).[5] Our findings are similar. Clarke et al found no correlation between pupillary adaptation in darkness and diabetes duration in diabetic children.[4] These conflicting results may be attributed to the effect of age, or to genuine population differences.

The effect of metabolic control on the development of autonomic neuropathy has been studied in adults. In terms of pupil size in darkness in subjects with short duration of disease (0–3 years),[19] autonomic damage to the iris appears to be reversible with improved metabolic control. Moreover Hreidarsson showed in adult diabetic subjects a strong inverse relationship between long term glycaemic control and pupil size.[9] Schwingshandl et al showed in diabetic adolescents a significant negative correlation of pupillary diameter with HbA1 and with blood glucose values.[5] Our findings are similar: pupillary diameter was significantly related to glycaemic control, expressed as the mean of HbA1 measurements over 18 months. The correlations were unaffected when controlling for diabetes duration. When dividing the diabetic population in to three groups differing in glycaemic control, the narrowest pupil diameter was found in the group with the highest HbA1 levels. Clarke et al reported no correlation between pupil diameter and glycaemic control in diabetic children, albeit based on single measurements of HbA1 and fructosamine.

	Abnormal (n=8)	Rest of the diabetic children (n=93)	p Value
Age (years)	14·3 (9·6–16·4)	13·8 (6·0–17·1)	NS
Sex (boys:girls)	4:4	45:48	
Duration (years)	9·2 (2·6–12·0)	3·7 (0·4–13·9)	0·004
Height SD score	−0·2 (−1·9 to 1·2)	0·2 (−2·1 to 2·3)	NS
Body mass index (kg/m²)	19·5 (15·0–25·4)	19·1 (14·3–27·2)	NS
HbA1 (%)	12·6 (10·9–16·3)	10·9 (7·4–18·1)	0·028
Diastolic blood pressure (SD score)	2·5 (1·5–4·4)	1·8 (−0·5 to 5·4)	NS
Albumin/creatinine ratio of daytime urine	1·4 (0·2–3·4)	0·5 (−1·0 to 2·8)	0·002
Pupil diameter (%)	54·8 (50·3–56·5)	63·4 (56·9–72·1)	0·0001

Pupillary dilatation in darkness correlated with other candidate tests of latent diabetes complications. Thus, in keeping with previous studies[4][13] pupil diameter was positively related to the blood pressure response to standing.

Relationships of pupillary variables with cardiovascular tests have been found in adults,[2] but not in children and adolescents with IDDM.[4][5] In keeping with the above studies, no correlation between pupillary diameter and cardiovascular tests was found in the Avon study. The different results between the above studies could be attributed to the complex involvement of sympathetic and parasympathetic pathways in different tests of autonomic function.

Overall, eight (7·9%) diabetic children and adolescents and four (3·9%) controls were found to have a pupillary diameter below the reference limit. These children had longer diabetes duration and poorer glycaemic control when compared with the rest of the diabetic population. Schwingshandl *et al* also identified 14/142 (9·8%) diabetic adolescents with pupillary adaptation below the reference range,[5] with similar characteristics to the ones reported in the Avon study. Clarke *et al* reported an increased prevalence (19%) of abnormal pupillary adaptation in a group of diabetic children with age range, diabetes duration, and glycaemic control similar to the Avon study and in 3·7% of the control children.[4] Thus, abnormalities of pupillary adaptation in darkness as an index of sympathetic neuropathy are not uncommon in childhood diabetes.

Previous studies have shown that parasympathetic impairment is also present in childhood diabetes. Mitchell *et al* reported abnormality in three heart rate tests in 7·8% diabetic children,[20] while Schwingshandl *et al* reported abnormality in two heart rate tests in 3·5% of diabetic adolescents.[5] In the Avon study, 8·7% of diabetic children were abnormal in two heart rate tests and 4·3% in three heart rate tests (unpublished data). Thus, although there are no clinical symptoms of autonomic neuropathy in children with IDDM, there is evidence that indices of both parasympathetic and sympathetic neuropathy are impaired.

Adult IDDM patients with symptomatic autonomic neuropathy have an increased mortality rate compared with the general diabetic population and are at risk of cardiorespiratory arrests with anaesthesia during minor operations.[21] It is not known whether asymptomatic neuropathy in diabetic children carries similar risks.

It has been shown in adults with diabetes in the early stages of neuropathy that abnormalities are reversible with improved glycaemic control.[22] The recent reports from the Diabetes Control and Complications Trial study underline the benefit of intensive therapy in preventing the appearance of clinical neuropathy.[23] Screening for autonomic dysfunction can therefore be justified in paediatric clinical practice, even among diabetic children with relatively short duration of disease. Identifying those with sympathetic impairment raises the prospect of targeting attempts to improve glycaemic control.

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